Preliminary data show that members of the FOXO family are expressed and functionally regulated in the developing myocardium. In vitro studies show that embryonic cardiac myocytes are responsive to growth factor stimulation, which results in the induction of the PI3K/AKT pathway, inactivation of FOXO proteins, and increased myocyte proliferation. These data support FOXO transcription factors as downstream effectors of PI3K/AKT signaling in cardiac myocytes and represent a novel approach to the investigation into the developmental regulation of cardiac myocyte proliferation. The generation of cardiac-specific FOXO transgenic mice and FOXO gene ablation studies using siRNA are currently in progress to further elucidate the role of FOXO factors in heart development.

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Mechanisms of caudal truncation in adrenocortical dysplasia (*acd*) mice

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Adrenocortical dysplasia (*acd*) is a spontaneous autosomal recessive mouse mutant with developmental defects in organs derived from the urogenital ridge: the kidneys, gonads, and adrenals. In addition, the *acd* mutation exhibits embryonic lethality on certain genetic strains, and analysis of *acd* mutant embryos reveals a striking embryologic phenotype that includes caudal truncation and axial skeletal patterning defects. We have previously characterized the *acd* mutation as a splicing defect in a gene (*Acd*) that encodes a novel component of the complex of telomere binding proteins that functions to maintain telomere integrity and regulate telomerase activity. Here, we report widespread expression of *Acd* mRNA in mouse embryos. We observed increased expression in the developing limb buds, tail, and neural tube, which resembles the embryonic expression pattern of the telomerase RNA component (*Terc*) gene and corresponds to the structural defects observed in *acd* mutant embryos. The function of ACD as a telomeric protein leads to the hypothesis that the mechanism leading to caudal truncation in *acd* mutant mice is via activation of p53, leading to apoptosis or cell cycle arrest. Preliminary studies reveal an increased number of TUNEL-positive cells in the caudal neural tube of *acd* embryos, but no gross differences in proliferation by PCNA immunohistochemistry, indicating that apoptosis is one mechanism leading to caudal truncation in *acd* mice. Further studies of proliferation and apoptosis in the caudal region of *acd* mutant embryos are currently in progress. This work was supported by NIH K08-HD42487 and the March of Dimes.

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Survival and differentiation of embryonic geniculate and trigeminal ganglia exposed at two stages to BMP-4 and noggin in vitro

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At rat embryonic day 13 (E13), nerve fibers from geniculate and trigeminal ganglia are within the early tongue. By E16, these ganglion cells innervate fungiform papillae and surrounding tongue epithelium, and thus are exposed to target-derived signaling factors. Bone morphogenetic protein 4 (BMP-4), known to be involved in neuron survival and differentiation, and its antagonist, noggin, are expressed in tongue by E13 and dramatically influence taste papilla development. To determine if these proteins affect the neurons that innervate tongue and papillae, we compared survival and neurite outgrowth in E13 and E16 geniculate and trigeminal ganglia explanted and cultured with exogenous BMP-4, noggin, or brain-derived neurotrophic factor (BDNF), a survival factor. Compared to geniculate ganglia exposed to BDNF, at E13 and E16, either BMP-4 or noggin resulted in a substantial decrease in neurons and neurite extension. The reduction was especially pronounced at E13. Survival and neurite extension also were decreased in E13 trigeminal neurons exposed to BMP-4 but were sustained by exposure to noggin. At E16, noggin continued to sustain a large population of trigeminal neurons, but BMP-4 was less effective at inhibiting survival. Thus, for the trigeminal ganglion a developmental shift in sensitivity to BMP-4 is evident. Geniculate and trigeminal ganglia display unique requirements for survival and differentiation factors during different developmental stages that perhaps relate to the heterogeneity of their respective neuronal populations.

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Differential regulation of male and female oligodendrocyte proliferation by hormones

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Sexual dimorphism has been established in gray matter regions of the brain and spinal cord. We recently showed that rodent white matter is sexually dimorphic (Cerghet et al., 2006). Moreover, exogenous hormones appear to regulate sexually dimorphic differences in turnover of oligodendrocytes (olgs) and myelin degradation in vivo. To investigate which hormones are involved, we treated enriched olg cultures from males and females grown in serum-free medium with different concentrations of estrogen (E2) and progesterone (P2), and counted the olgs after 4 days of exposure to hormones. The numbers of olgs increased 1.5× with 2.5 nM and 2× with 5